

**c.) Remarks**

The specification has been amended at page 6, As of this response, claims 20, 22, and 24 remain pending. A listing of the outstanding rejections follow. Applicants address each one in turn.

**Outstanding Rejections/Objections**

The Examiner has entered or maintained the following objections/rejections:

1. Claims 20, 22-24, 26-28, and 35 are rejected under 35 USC § 112, first paragraph.
2. Claims 20, 22-24, 26-28, and 35 are rejected under 35 USC § 112, second paragraph.
3. Claims 20, 22-24, 26-28, and 35 are rejected under 35 USC § 102(b) or 102(e), as being anticipated by WO 96/14419 to Flitsch et al (Flitsch PCT '419) , or U.S. Patent 6,100,074 (Flitsch '074). Flitsch '074 is the U.S. equivalent of Flitsch PCT '419.
4. Claims 20, 22-24, 26-28, and 35 are rejected under the judicially created doctrine of double patenting over claims 8 of U.S. Patent 6,100,074.

**Rejection under 35 USC § 112, First Paragraph**

The Examiner asserts that 20, 22-24, 26-28, and 35 contain subject matter not described in the specification as required under 35 USC § 112, first paragraph. Claim 20 has been amended to introduce the following features. The substrate has been limited to the particular compounds of previous claim 27, the enzyme has been limited to a P450cam enzyme, a reference to SEQ ID NO:2 has been introduced and, a reference to a mutation at position 295 has been introduced based on support found at page 7, line 17 of the application.

Because base claim 20 now recites specific substrates for oxidation (i.e., those in the previous claim 27), and is limited to a P450cam enzyme, Applicants believe that the Examiner's rejection with respect to this point has been obviated by the present amendment of remaining claims 20, 22, and 24. Additionally, the examples provided in the application show the oxidation of such compounds by P450cam. Thus, Applicants respectfully assert that the invention is sufficiently described in the application, and the applicants were in possession of the invention at the filing date and that the requirements of § 112, first paragraph are satisfied. Accordingly, Applicants respectfully request that the Examiner withdraw the outstanding rejection under 35 USC § 112, first paragraph and allow the pending claims.

*Rejection under 35 USC § 112, Second Paragraph*

The Examiner asserts that claims 20, 22-24, 26-28, and 35 lack definiteness as required under 35 USC § 112, second paragraph. The Examiner has asserted that, without a reference to a specific SEQ ID NO., the references to specific mutational modifications remains indefinite.

Applicants have amended base claim 20 to refer to a specific SEQ ID NO. In this way, the basis for the Examiner's rejection has been addressed. By amending the base independent claim, the basis for this rejection falls away in all of the pending claims. In light of this, Applicants respectfully request that the Examiner withdraw the outstanding rejection under 35 USC § 112, second paragraph and allow the pending claims.

*Rejection under 35 USC § 102(b) or (e)*

The Examiner has rejected claims 20, 22-24, 26-28, and 35 under 35 USC § 102(b) or (e) as being anticipated by Flitsch et al, WO 96/14419 and U.S. equivalent Patent No. 6,100,074 (collectively referred to herein as "Flitsch"). Flitsch does not disclose the specific

compounds mentioned in amended base claim 20, but merely refers to "halogenated variants" of broad groups of compounds. The only specific halogenated compound which is disclosed in Table 4g of Flitsch is a hexane derivative and not an aromatic compound. Therefore the present claims are novel over Flitsch.

It must also be noted that much of the data presented in Flitsch is for the purpose of demonstrating differences between the mutant and wild-type enzymes (in particular see Table 2 of the documents). Thus although differences can be seen in spin states between the two types of enzyme when they are contacted with different substrates, whether actual oxidation occurs is not clear from much of the data. NADH turnover is not shown for most substrates, and in particular there is on the whole no analysis of oxidation products to show the production of oxidised substrates, as is the case with Table 4g. Thus it is not clear whether this means that oxidation is not occurring. While the data may demonstrate differences between the mutant and wild-type enzymes (for example in ability to switch spin states) the documents leave the skilled person in doubt as to the actual ability of the mutant P450 enzyme to oxidise many of the listed substrates. Based on the disclosure of Flitsch et al the skilled person could not come to the general conclusion that the mutant P450 enzymes mentioned in the document had superior abilities to oxidise substrates.

Given that Flitsch et al provides no data at all describing the successful oxidation of a halogenated aromatic compound it is certainly not possible to predict from this document whether any of the compounds recited in amended base claim 20 could be successfully oxidised by a mutant P450cam enzyme. The oxidation of ring carbons of polychlorinated aromatic compounds is difficult. In order to illustrate this point, we enclose print outs of information which is available at the following websites:

[http://www.nwhc.usgs.gov/pub\\_metadata/field\\_manual/chapter\\_41.pdf](http://www.nwhc.usgs.gov/pub_metadata/field_manual/chapter_41.pdf)

[http://en.wikipedia.org/wiki/Polychlorinated\\_biphenyl](http://en.wikipedia.org/wiki/Polychlorinated_biphenyl)

As can be seen this discusses the chemical stability of polychlorinated aromatic compounds, and the consequent environmental problems which can occur. This issue is also discussed on page 1 of the instant application. Thus the skilled person would be aware of the chemical inertness of polychlorinated aromatic compounds, and would not automatically assume from the disclosure of Flitsch that mutant P450cam enzymes would be capable of oxidising such compounds. Flitsch simply provides no teaching or suggestion of this.

The present invention is based on the finding that substituting particular amino acids of a P450 enzyme dramatically increases its activity towards particular polychlorinated aromatic compounds. As can be seen from the table on page 23 of the instant application, although wild-type P450cam has negligible activity towards polychlorinated aromatic compounds, a P450cam enzyme with mutations at the positions recited in amended base claim 20 has substantially increased activity towards such substrates. Flitsch has no teaching which discloses or suggests this increased activity towards polychlorinated aromatic substrates. Therefore, in light of the amendments and arguments presented in this response, Applicants assert that the pending claims are novel and inventive over this Flitsch. Accordingly, Applicants respectfully request that the Examiner remove the outstanding rejection under § 102(b)/(e) with respect to the currently pending claims.

*Rejection for Non-Statutory Double Patenting*

The Examiner has rejected claims 20, 22-24, 26-28, and 35 for non-statutory double patenting over claims 8 of U.S. Patent 6,100,074 (Flitsch). Applicants assert that the amendments and arguments made herein distinguish the presently pending claims from claim 8 of Flitsch. In the immediately preceding section of this response, Applicants have

demonstrated that the presently pending claims are not anticipated nor rendered obvious by any of Flitsch, including claim 8.

Importantly, nowhere in the Markush group of claim 8 of Flitsch are recited the specific compounds mentioned in amended base claim 20. Claim 8 merely refers to "halogenated variants" of broad groups of compounds. The only specific halogenated compound which is disclosed in Table 4g of Flitsch is a hexane derivative and not an aromatic compound. Therefore the present claims are nonobvious in light of claim 8 of Flitsch. The Examiner is directed to the remainder of the discussion regarding Flitsch in the immediately preceding section of this response. In light of the arguments with respect to Flitsch and the amendments of the present response, Applicants respectfully request that the Examiner withdraw the outstanding rejection for non-statutory double patenting and allow the pending claims.

**d.) Conclusions**

Claims 20, 22, and 24 remain pending as of this Preliminary Amendment. In light of the amendments and arguments made herein, Applicants assert that all of the Examiner's rejections have been addressed and that the pending claims are now in condition for allowance. Because the Examiner's rejections have been properly addressed, Applicants respectfully request withdrawal of the outstanding rejections and earnestly request allowance of the application. This is intended to be a complete response to the outstanding rejections. If any issues remain outstanding, please contact the undersigned for resolution of the same.

Applicants are including with this response payment for a Request for Continued Examination as per 37 CFR 1.17(e) [\$770.00]. Applicants believe that no other fees are due or associated with the filing of this document. However, if Applicants are in error, the Commissioner is hereby authorized to draw any additional fees associated with this filing from Deposit Account No. 06-2375, under Order No. P02353US1/10112404, from which the undersigned is authorized to draw.

Respectfully submitted,

Date: March 29, 2004

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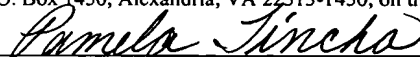
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Date: March 29, 2004

By



(Pamela Tincha)

# Polychlorinated biphenyl

From Wikipedia, the free encyclopedia.

**Polychlorinated biphenyls** (PCBs) are a class of organic compounds with 1 to 10 chlorine atoms are attached to biphenyl and a general structure of  $C_{12}H_{10-x}Cl_x$ . Most PCB congeners are colorless, odorless crystals. The commercial mixtures are clear viscous liquids (the more highly chlorinated mixtures are more viscous, for example, Aroclor 1260 is a "sticky resin"). Although the physical and chemical properties vary widely across the class, PCBs have low water solubilities and low vapor pressures. They are soluble in most organic solvents, oils, and fats. PCBs are very stable compounds and do not degrade easily. However, under certain conditions they may be destroyed by chemical, thermal, and biochemical processes. These processes may occur intentionally (e.g., incineration), unintentionally, or metabolically. Because of their high thermodynamic stability, all degradation mechanisms are difficult. Intentional degradation as a treatment of unwanted PCBs generally requires high heat or a catalysis. Environmental and metabolic degradation generally proceeds quite slowly relative to most other compounds.

PCBs were commercially produced as complex mixtures containing multiple isomers at different degrees of chlorination for a variety of applications, including dielectric fluids for capacitors and transformers, heat transfer fluids, hydraulic fluids, lubricating and cutting oils, and as additives in pesticides, paints, carbonless copy ("NCR") paper, adhesives, sealants, and plastics. The major producer, Monsanto, marketed PCBs under the trade name Aroclor from 1930 to 1977. Their commercial utility was based largely on their chemical stability, including low flammability, and desirable physical properties, including electrical insulating properties. Their chemical and physical stability has also been responsible for their continuing low-level persistence in the environment, and the lingering interest decades after regulations were imposed to control environmental contamination.

In the 1970s, their use declined and essentially terminated because of environmental concerns. PCBs have entered the environment through both use and disposal. The environmental transport of PCBs is complex and global. The public, legal, and scientific concerns about PCBs arose from research indicating they were environmental contaminants that had a potential to adversely impact the environment, and, therefore, were undesirable as commercial products. The extent to which PCBs are toxic remains controversial. Despite active research spanning five decades, extensive regulatory actions, and an effective ban on their production since the 1970s, PCBs remain a focus of environmental attention.

## Health effects

The most commonly observed health effects in people exposed to large amounts of PCBs are skin conditions such as acne and rashes. Studies in exposed workers have shown changes in blood and urine that may indicate liver damage. PCB exposures in the general population are not likely to result in skin and liver effects. Most of the studies of health effects of PCBs in the general population examined children of mothers who were exposed to PCBs.

Animals that ate food containing large amounts of PCBs for short periods of time had mild liver damage and some died. Animals that ate smaller amounts of PCBs in food over several weeks or months developed various kinds of health effects, including anemia; acne-like skin conditions; and liver, stomach, and thyroid gland injuries. Other effects of PCBs in animals include changes in the immune system, behavioral alterations, and impaired reproduction.

PCBs are not known to cause birth defects.

Few studies of workers indicate that PCBs were associated with certain kinds of cancer in humans, such as cancer of the liver and biliary tract. Rats that ate food containing high levels of PCBs for two years developed liver cancer. The Department of Health and Human Services (DHHS) has concluded that PCBs may reasonably be anticipated to be carcinogens. The EPA and the International Agency for Research on Cancer (IARC) have determined that PCBs are probably carcinogenic to humans.

Women who were exposed to relatively high levels of PCBs in the workplace or ate large amounts of fish contaminated with PCBs had babies that weighed slightly less than babies from women who did not have these exposures. Babies born to women who ate PCB-contaminated fish also showed abnormal responses in tests of infant behavior. Some of these behaviors, such as problems with motor skills and a decrease in short-term memory, lasted for several years. Other studies suggest that the immune system was affected in children born to and nursed by mothers exposed to increased levels of PCBs. There are no reports of structural birth defects caused by exposure to PCBs or of health effects of PCBs in older children. The most likely way infants will be exposed to PCBs is from breast milk. Transplacental transfers of PCBs were also reported. In most cases, the benefits of breast-feeding outweigh any risks from exposure to PCBs in mother's milk.

*Retrieved from "[http://en.wikipedia.org/wiki/Polychlorinated\\_biphenyl](http://en.wikipedia.org/wiki/Polychlorinated_biphenyl)"*

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## Chapter 41

# Polychlorinated Biphenyls

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### Synonyms

*PCBs, aroclors, chlorinated biphenyls*

Polychlorinated biphenyls (PCBs) are industrial compounds with multiple industrial and commercial uses (Table 41.1). PCBs are chemically inert and stable when heated. These properties contribute greatly to PCBs having become environmental contaminants. The chemical inertness and heat stability properties that make PCBs desirable for industry also protect them from destruction when the products in which they are used are discarded. These same properties also enable PCB residues to persist in the environment for long periods of time and to be transported worldwide when contaminated particulate matter travels through waters, precipitation, wind, and other physical forces.

PCBs have a physical structure similar to DDT, and, like DDT, they are classified as aromatic hydrocarbons which contain one or more benzene rings. The presence of chlorine results in DDT, PCBs, and other compounds with similar structures commonly being referred to as chlorinated hydrocarbons. The toxicity of these compounds is associated with the amount of chlorine they contain. The trade name of Aroclor® for PCBs that were produced by a manufacturer in the United States contains a numerical designation that specifies the amount of chlorine present in a particular formulation. For example, Aroclor® 1221 contains 21 percent chlorine while Aroclor® 1254 contains 54 percent chlorine. The first two digits designate the number of carbons in the formulation. The chemical structure of PCBs results in the possibility of many different forms or isomers, (more commonly called congeners) of these compounds. PCBs in other countries have different trade names than Aroclor® (Table 41.2).

### Cause

Like other chlorinated hydrocarbons, PCBs accumulate in the fat of animals or are lipophilic, and they tend to become concentrated at higher levels of the food chain. In general, persistence increases for PCBs that are made with higher amounts of chlorine. Birds are most susceptible to PCB compounds of the mid-chlorination range (42–54 percent).

### Species Affected

Mammals, especially mink, are more susceptible than birds and invertebrates to direct toxicity from PCBs. The highest tissue concentrations of these compounds are found among birds, especially marine species that are at the top of complex oceanic food webs and among fish-eating birds, such

as cormorants, that use large inland water bodies. For example a 12.9-fold increase has been reported from plankton to fish in a Lake Michigan food web. Although direct toxicity for birds is generally low (Table 41.3), PCBs are powerful inducers of liver enzyme systems that increase the metabolism of hormones. PCBs may have caused thin eggshells in double-crested cormorants and white pelicans, and under experimental conditions, in ring-doves and (perhaps) in Coturnix quail and mallard ducks. Unfortunately, there is insufficient knowledge to clearly define the impacts of PCBs on bird reproduction, especially in field situations, because tissue residues are often highly correlated with other lipophilic compounds, such as organochlorines. Findings have generally been inconclusive, but the greatest effects have been seen in gallinaceous birds such as pheasants, chickens, and doves.

### Distribution

PCBs were first identified in the tissues of wildlife in Sweden, and they are now known to occur in a wide variety of wildlife and other species, including humans, throughout the world. PCBs are clearly global contaminants, and they are the most abundant of the chlorinated hydrocarbon pollutants in the global ecosystem with the possible exception of petroleum products. Industrial wastes released into aquatic systems, point sources of contamination from manufacturing facilities, landfills receiving waste from such facilities, and combustion and other disposal of products containing PCBs are generally recognized sources of contamination. Another less well-known source of PCB contamination of the environment was the use of PCBs during the 1950s and 1960s as additives to extend the residual life and effectiveness of expensive chlorinated insecticides such as chlordane, aldrin, dieldrin, and benzene hexachloride. It is estimated that more than 1.5 metric tons of PCBs have been produced worldwide. PCB manufacturing in the United States was discontinued in 1978.

The variable environmental distribution of PCBs results from their physical and chemical properties, which influence their rates of distribution, retention, and degradation in different environments. This results in great differences in the relative concentrations of the different forms of PCBs found in wildlife samples from different geographic areas and is also a reflection of the magnitude of local and regional con-

**Table 41.1** *Uses of polychlorinated biphenyls (PCBs) in industry and products for society.*

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**Properties**

Heat stability  
Chemical stability  
Ability to be mixed with organic compounds  
Slow degradation

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**Industrial uses**

Lubricants, hydraulic fluids, grinding fluids  
Heat transfer agents, insulators  
Plasticizers  
Dielectric sealants  
Dedusting agents  
Protective coatings

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**Common products that have contained PCB additives**

Wire and cable coating  
Impregnants for braided cotton-asbestos insulation  
Printing inks and mimeograph inks  
Preparation of imitation gold leaf  
Pigment vehicle for decoration of glass and ceramics  
Essential components of coating for flameproofing cotton drill for outer garments and for rendering olive-drab canvas fire retardant, water-repellant, and rot-proof (tents, tarpaulins)  
Moistureproof coating for wood, paper, concrete, and brick  
Asphalt, roof coatings  
High quality precision casting wax; waxes used in making dental castings and costume jewelry  
Sealers for masonry, wood, fiberboard, and paper  
Window envelopes  
Polystyrene, polyethylene, neoprene, polybutene, silicone rubber, crepe rubber  
Plasticizers in paints  
Life extenders and sometimes toxicity synergists for pesticides containing DDT, dieldrin, lindane, chlordane, aldrin, and benzene

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tamination patterns, environmental transport processes, and the composition of PCB residues in the food chain.

## Seasonality

Exposure to PCBs is not seasonally dependent; except that in warm weather, PCB residues may vaporize or evaporate with liquid from contaminated areas, and thus, increase the risk of airborne exposure.

## Field Signs

Direct mortality of wild birds from exposure to PCBs rarely occurs. We are only aware of one such event having been documented. The number of different PCBs present in the environment further complicates evaluations because of different impacts and lethality associated with these different compounds. Nonspecific signs associated with acute exposure of birds to toxic levels of PCBs include lethargy, lack

of locomotive and muscle coordination or ataxia, tremors, and other observations. Behavioral modifications and impaired reproductive performance may also occur and would be more readily detected at the population rather than individual level (Table 41.4).

## Gross Lesions

There are no diagnostic lesions associated with exposure to PCBs. Enlarged liver and kidneys, atrophy of the spleen and the bursa of Fabricius, emaciation, and excess fluids around the heart have been associated with chronic exposure.

Excess fluid or edema in tissues has been found in some cases of acute PCB exposure, and this suggests that PCBs may interfere with tissue permeability or cardiac function or both. PCBs have been shown to cause physical defects in embryos, or be teratogenic, in chickens, and they also cause

**Table 41.2** Trade names for polychlorinated biphenyls (PCBs).

Trade name	Country of manufacturer	Manufacturer
Aroclor®	United States of America	Monsanto
Clophens®	Germany	Bayer
Fenclores®	Italy	Caffaro
Phenoclores®; Pyralenes®	France	Prodelec
Kanechlores®	Japan	Kanegafuchi
Others have been produced in Czechoslovakia and the former USSR		

**Table 41.3** Relative toxicity of polychlorinated biphenyls (PCBs) for birds. [Adapted from Eisler, 1986.  $LC_{50}$  is the contaminant concentration in the diet that is required to kill 50 percent of the test animals in a given period of time; by comparison, the  $LC_{50}$  for mink to Aroclors® 1242 and 1254 is 8.6 and 6.7, respectively. mg/kg, milligrams per kilogram. >, greater than. —, no data available.]

Species	$LD_{50}$ (mg/kg of Aroclor®)			
	1221	1242	1254	1260
Bobwhite quail	>6,000	2,098	604	747
Mallard duck	—	3,182	2,699	1,975
Ring-necked pheasant	>4,000	2,078	1,091	1,260
Japanese quail	>6,000	>6,000	2,898	2,186
European starling, red-winged blackbird, brown-headed cowbird	—	—	1,500	—

**Table 41.4** *Reported effects of polychlorinated biphenyls (PCBs) in birds.*

Type of impact	Examples
Behavioral	Lethargy Locomotive and muscle incoordination or ataxia Tremors and convulsions Reduced nest attentiveness and protection of eggs
Reproductive	Embryo mortality resulting in decreased hatchability of eggs Decreased egg production Egg shell thinning
Pathological	Accumulation of fluid within the pericardial sac or hydropericardium Excess fluid or edema in body tissues and organs Atrophy of bursa of Fabricius, spleen, and other lymphoid tissues Enlarged livers that are firm and light colored Bill and foot deformities (from embryonic exposure)
Immunological	Increased susceptibility to infectious disease
Other	Weight loss Debilitation

a condition analogous to chick edema disease. This condition results in the leakage of body fluids into various organs and tissues. However, the presence of dioxins as contaminants within the PCB formulations may be the actual cause of these lesions.

### Diagnosis

Diagnosis of acute poisoning is based on PCB residues in tissues, and as for most other chlorinated hydrocarbons, mortality is best diagnosed from residues found in brain tissue. However, the concentrations of PCBs that indicate poisoning vary greatly with the specific formulation of PCBs, the species of bird, and, often, the presence of other environmental contaminants. Detection of subacute effects, such as poor reproductive performance and immunosuppression, is also confounded by these same factors. Comparison of residues in the tissues of birds suspected of being poisoned with residues in tissues of normal birds of the same species in nearby or regional sites can be diagnostically useful along with knowledge of PCB deposition and discharges in the area. Comparisons are sometimes difficult because of the varying effects of different PCB mixtures and the interactions that occur between PCBs, other pollutants, and other disease agents. Many toxic and biochemical responses from PCB exposure occur in multiple species and body organ systems.

Residue levels alone will generally not be sufficient data for making a diagnosis. Necropsy findings combined with laboratory analyses, including residue evaluations, knowledge of environmental conditions and events at the field site, and response of different species to PCB exposure are all needed for sound judgements to be reached.

### Control

Prevention of the entry of PCBs into the environment and containment or removal of PCB contamination that is already present are necessary to reduce exposure of wildlife. PCB sales in the United States were stopped in the 1970s, but large amounts are still present in the environment due to environmental persistence and to global transport by winds and other means from locations where PCBs are still used. Improper disposal of products that contain PCBs through landfills and incineration at temperatures that are too low (below 1,600 °C) to destroy PCBs can cause further environmental contamination. However, more stringent air-quality standards in the United States and other nations have diminished the potential that PCBs in incinerated materials will be added to the environment through combustion.

Bird use of heavily contaminated sites should be prevented to the extent feasible by habitat manipulation, physical barriers, scaring devices, and other appropriate means. Knowl-

edge of PCB levels in specific environments should be gained prior to developing those areas for wildlife, including the use of dredge material to create artificial islands for bird nesting habitat. PCB and heavy metal loads in sediments should also be considered in decisions regarding dumping dredge materials.

## Human Health Considerations

PCBs are known to accumulate in humans, and health advisories are often issued about consuming wildlife from heavily contaminated environments. Residues in wildlife can only be transferred to humans by consuming contaminated tissues. As with most chlorinated hydrocarbons, the greatest concentrations of residues are in fat tissue, and removing fatty parts of the carcass prior to cooking can significantly reduce potential human exposure. Although PCB residues cannot be transferred to humans from wildlife by means other than consumption, the cause of death is seldom known when dead wildlife are encountered and the risk of exposure to disease agents that can be transmitted by contact should not be taken. Always wear gloves or use other physical barriers to prevent personal contact with the carcass.

*Milton Friend and J. Christian Franson*

## Supplementary Reading

- Eisler, R., 1986, Polychlorinated biphenyl hazards to fish, wildlife, and invertebrates: a synoptic review: Fish and Wildlife Service Biological Report 85(1.7), 72 p.
- Hoffman, D.J., Rice, C.P., and Kubiak, T.J., 1996, PCBs and dioxins in birds, *in* Beyer, W.N., and others, eds., *Environmental contaminants in wildlife: interpreting tissue concentrations*: Boca Raton, Fla., Lewis Publishers, p. 165–207.
- O'Hara, T.M., and Rice, C.D., 1996, Polychlorinated biphenyls, *in* Fairbrother, A., and others, eds., *Noninfectious diseases of wildlife* (2nd ed.): Ames, Iowa, Iowa State University Press, p. 71–86.
- Rice, C.P., and O'Keefe, P., 1995, Sources, pathways, and effects of PCBs, dioxins, and dibenzofurans, *in* Hoffman, D.J., and others, eds., *Handbook of ecotoxicology*: Boca Raton, Fla., Lewis Publishers, p. 424–468.